UnitedHealthcare Oxford

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Clinical Policy

VAGUS NERVE STIMULATION

Policy Number: SURGERY 073.16 T2 **Effective Date**: January 1, 2019

Instructions for Use

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Related Policies

- Bariatric Surgery
- Deep Brain and Cortical Stimulation
- Implanted Electrical Stimulator for Spinal Cord
- Transcranial Magnetic Stimulation

CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General benefits package
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes[1,2]
Precertification with Medical Director Review Required	No[1]
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Inpatient, Outpatient, Office[2]
Special Considerations	[1]Medical Director review is required for any diagnosis/indication not listed in the Payment Guidelines section of this policy (excluding the electronic analysis codes). [2]**Participating providers in the office setting**: Precertification is required for services performed in the office of a participating provider. **Non-participating/ out-of-network providers in the office setting**: Precertification is not required, but is encouraged for out-of-network services performed in the office. If precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered.

COVERAGE RATIONALE

Implantable vagus nerve stimulators are proven and medically necessary for treating epilepsy in individuals with ALL of the following (see below for implants that allow detection and stimulation of increased heart rate):

- Medically refractory epileptic seizures with failure of two or more trials of single or combination antiepileptic drug therapy or intolerable side effects of antiepileptic drug therapy; and
- The individual is not a surgical candidate or has failed a surgical intervention; and
- No history of left or bilateral cervical vagotomy. The U.S. Food and Drug Administration (FDA) identifies a history of left or bilateral cervical vagotomy as a contraindication to vagus nerve stimulation.

Implantable vagus nerve stimulators are unproven and not medically necessary for treating ALL other conditions due to insufficient evidence of efficacy. These conditions include but are not limited to:
- Alzheimer's disease
- Anxiety disorder
- Autism spectrum disorder
- Back and neck pain
- Bipolar disorder
- Bulimia
- Cerebral palsy
- Chronic pain syndrome
- Cluster headaches
- Depression
- Fibromyalgia
- Heart failure
- Migraines
- Morbid obesity
- Narcolepsy
- Obsessive-compulsive disorder
- Paralysis agitans
- Sleep disorders
- Tourette's syndrome

The following are unproven and not medically necessary due to insufficient evidence of efficacy:
- Vagus nerve stimulation implants that allow detection and stimulation of increased heart rate (e.g., AspireSR™ Model 106) for treating epilepsy.
- Transcutaneous (nonimplantable) vagus nerve stimulation for treating all indications.

Note: For vagus nerve blocking for the treatment of obesity, refer to the Clinical Policy titled Bariatric Surgery.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

CPT Code	Description
61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
64568	Incision for implantation of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
64570	Removal of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator

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HCPCS Code	Description
E0770	Functional electrical stimulator, transcutaneous stimulation of nerve and/or muscle groups, any type, complete system, not otherwise specified
E1399	Durable medical equipment, miscellaneous
L8679	Implantable neurostimulator, pulse generator, any type
L8680	Implantable neurostimulator electrode , each
L8682	Implantable neurostimulator radiofrequency receiver
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
L8686	Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension

HCPCS Code	Description
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension

DESCRIPTION OF SERVICES

The vagus nerve, a large nerve in the neck, connects the lower part of the brain to the heart, lungs and intestines. Vagus nerve stimulation (VNS) uses short bursts of electrical energy directed into the brain via the vagus nerve. Implantable vagus nerve stimulators are implanted subcutaneously in the upper chest. These systems include a pulse generator/neurostimulator and electrode that deliver pulses of current to the left vagus nerve. Following implantation, the generator is programmed to stimulate the vagus nerve at a rate determined by the individual and physician. These devices generally have two types (modes) of stimulation: normal (the device stimulates according to preset parameters) and magnet (gives a single, on-demand stimulation). It is an expectation that the physician have experience and expertise in the use of vagus nerve stimulation.

The AspireSR Model 106 (Cyberonics now known as LivaNova) is an implantable vagus nerve stimulation generator that has an additional, optional mode called AutoStim Mode or Automatic Stimulation. This mode monitors and detects tachycardia heart rates, which may be associated with an impending seizure, and automatically delivers stimulation to the vagus nerve. The effect of the AutoStim Mode on reducing the number of seizures is being evaluated.

Nonimplantable VNS devices [also referred to as n-VNS or transcutaneous VNS (t-VNS)] are being investigated as a noninvasive alternative to implantable VNS for indications such as pain, epilepsy, tinnitus, and depression. An example of this type of device is gammaCore (ElectroCore, LLC) which is a noninvasive handheld prescription device intended to deliver transcutaneous vagus nerve stimulation for the acute treatment of pain associated with episodic cluster headache.

CLINICAL EVIDENCE

Implantable Vagus Nerve Stimulators

Epilepsy

In a Cochrane review, Panebianco et al. (2015) evaluated the current evidence for the efficacy and tolerability of vagus nerve stimulation when used as an adjunctive treatment for people with drug-resistant partial epilepsy. Five randomized controlled trials (439 participants) were included in the review. The authors concluded that VNS for partial seizures appears to be an effective and well tolerated treatment in 439 included participants from five trials. Results of the overall efficacy analysis show that VNS stimulation using the high stimulation paradigm was significantly better than low stimulation in reducing frequency of seizures. Results for the outcome "withdrawal of allocated treatment" suggest that VNS is well tolerated as withdrawals were rare. Adverse effects associated with implantation and stimulation were primarily hoarseness, cough, dyspnea, pain, paresthesia, nausea and headache, with hoarseness and dyspnea more likely to occur on high stimulation than low stimulation.

Englot et al. (2016) examined rates and predictors of seizure freedom with VNS. The investigators examined 5554 patients from the VNS therapy Patient Outcome Registry, and also performed a systematic review of the literature including 2869 patients across 78 studies. Registry data showed a progressive increase over time in seizure freedom after VNS therapy. Overall, 49% of patients responded to VNS therapy 0 to 4 months after implantation (≥50% reduction seizure frequency), with 5.1% of patients becoming seizure-free, while 63% of patients were responders at 24 to 48 months, with 8.2% achieving seizure freedom. On multivariate analysis, seizure freedom was predicted by age of epilepsy onset >12 years, and predominantly generalized seizure type, while overall response to VNS was predicted by nonlesional epilepsy. Systematic literature review results were consistent with the registry analysis: At 0 to 4 months, 40.0% of patients had responded to VNS, with 2.6% becoming seizure-free, while at last follow-up, 60.1% of individuals were responders, with 8.0% achieving seizure freedom.

Kawai et al. (2017) reported the overall outcome of a national, prospective registry that included all patients implanted in Japan. The registry included patients of all ages with all seizure types who underwent VNS implantation for drug-resistant epilepsy in the first three years after approval of VNS in 2010. The registry excluded patients who were expected to benefit from resective surgery. Efficacy analysis was assessed based on the change in frequency of all seizure types and the rate of responders. Changes in cognitive, behavioral and social status, quality of life (QOL), antiepileptic drug (AED) use, and overall AED burden were analyzed as other efficacy indices. A total of 385 patients were initially registered. Efficacy analyses included data from 362 patients. Age range at the time of VNS implantation was 12 months to 72 years; 21.5% of patients were under 12 years of age and 49.7% had prior epilepsy surgery. Follow-up rate was >90%, even at 36 months. Seizure control improved over time with median seizure reduction of

25.0%, 40.9%, 53.3%, 60.0%, and 66.2%, and responder rates of 38.9%, 46.8%, 55.8%, 57.7%, and 58.8% at three, six, 12, 24, and 36 months of VNS therapy, respectively. There were no substantial changes in other indices throughout the three years of the study, except for self/family-accessed QOL which improved over time. No new safety issues were identified. The authors concluded that this prospective national registry of patients with drug-resistant epilepsy, with >90% follow-up rate, indicates long-term efficacy of VNS therapy which increased over time, over a period of up to three years.

In the PuLsE trial, Ryvlin et al. (2014) compared outcomes between patients receiving best medical practice (BMP) alone, and those treated with VNS in addition to BMP (VNS+BMP). In a randomized group of 96 patients, significant between-group differences in favor of VNS + BMP were observed regarding improvement in health-related quality of life, seizure frequency, and Clinical Global Impression-Improvement scale (CGI-I) score. More patients in the VNS + BMP group (43%) reported adverse events (AEs) versus BMP group (21%), a difference reflecting primarily mostly transient AEs related to VNS implantation or stimulation. According to the authors, this data suggests that VNS as a treatment adjunct to BMP in patients with pharmacoresistant focal seizures was associated with a significant improvement in health-related quality of life compared with BMP alone.

In a 2012 clinical guideline for the diagnosis and management of epilepsy, the National Institute for Health and Care Excellence (NICE) stated that vagus nerve stimulation is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults, children, and young people who are refractory to antiepileptic medication but who are not suitable for resective surgery. This includes adults, children and young people whose epileptic disorder is dominated by focal seizures (with or without secondary generalization) or generalized seizures. (NICE 2012, Updated April 2018)

AspireSR for Vagus Nerve Stimulation

Hamilton et al. (2018) compared the efficacy of AspireSR to preceding VNS battery models for battery replacements, and evaluated the efficacy of the AspireSR for new implants. Data were collected retrospectively from patients with epilepsy who had VNS AspireSR implanted over a three-year period between June 2014 and June 2017 by a single surgeon. Cases were divided into two cohorts, those in whom the VNS was a new insertion, and those in whom the VNS battery was changed from a previous model to AspireSR. Within each group, the seizure burden was compared between the periods before and after insertion of AspireSR. Fifty-one patients with a newly inserted AspireSR VNS model had a significant reduction in seizure frequency, with 59% (n = 30) reporting ≥50% reduction. Of the 62 patients who had an existing VNS, 53% (n = 33) reported ≥50% reduction in seizure burden when the original VNS was inserted. After the battery was changed to the AspireSR, 71% (n = 44) reported a further reduction of ≥50% in their seizure burden. The size of this reduction was at least as large as that resulting from the insertion of their existing VNS in 98% (61/62) of patients. The authors indicated that the results suggest that approximately 70% of patients with existing VNS insertions could have significant additional benefit from cardiac based seizure detection and closed loop stimulation from the AspireSR device. According to the authors, this study was a retrospective analysis and they reported patients' and carers' interpretation of their response to VNS therapy rather than by prospectively collected seizure diaries or a formal quality of life assessment tool. This retrospective seizure reporting was therefore a potential source of recall bias. The authors indicated that the lack of blinding and randomization could have resulted in selection bias as patients who were more likely to have had benefit from VNS therapy were offered treatment with AspireSR.

Boon et al. (2015) investigated the performance of a cardiac-based seizure detection algorithm (CBSDA) that automatically triggers VNS. Thirty-one patients with drug resistant epilepsy were evaluated in an epilepsy monitoring unit (EMU). Sixty-six seizures (n=16 patients) were available from the EMU for analysis. In 37 seizures (n=14 patients) a ≥ 20% heart rate increase was found and 11 (n=5 patients) were associated with ictal tachycardia (iTC). Multiple CBSDA settings achieved a sensitivity of ≥ 80%. False positives ranged from 0.5 to 7.2/hour. A total of 27/66 seizures were stimulated within ± 2 min of seizure onset. In 10/17 of these seizures, where triggered VNS overlapped with ongoing seizure activity, seizure activity stopped during stimulation. Physician-scored seizure severity (NHS3-scale) showed significant improvement for complex partial seizures (CPS) at EMU discharge and through 12 months. Patient-scored seizure severity (total SSQ score) showed significant improvement at 3 and 6 months. Quality of life (QOL) showed significant improvement at 12 months. The responder rate at 12 months was 29.6% (n=8/27). Safety profiles were comparable to prior VNS trials. The authors concluded that the investigated CBSDA has a high sensitivity and an acceptable specificity for triggering VNS. According to the authors, despite the moderate effects on seizure frequency, combined open-and closed-loop VNS may provide valuable improvements in seizure severity and QOL in refractory epilepsy patients. The significance of this study is limited by small sample size and short follow-up period. This study was sponsored by Cyberonics, Inc., the manufacturer of AspireSR.

Fisher et al. (2016) evaluated the performance, safety of the Automatic Stimulation Mode (AutoStim) feature of the Model 106 Vagus Nerve Stimulation (VNS) Therapy System during a 3-5-day Epilepsy Monitoring Unit (EMU) stay and long-term clinical outcomes of the device stimulating in all modes. This study was a prospective, unblinded, U.S. multisite study of the AspireSR in patients with drug-resistant partial onset seizures and history of ictal tachycardia.

VNS Normal and Magnet Modes stimulation were present at all times except during the EMU stay. Outpatient visits at 3, 6, and 12 months tracked seizure frequency, severity, quality of life, and adverse events. Twenty implanted patients (ages 21-69) experienced 89 seizures in the EMU. A total of 28/38 (73.7%) of complex partial and secondarily generalized seizures exhibited ≥20% increase in heart rate change. A total of 31/89 (34.8%) of seizures were treated by Automatic Stimulation on detection; 19/31 (61.3%) seizures ended during the stimulation with a median time from stimulation onset to seizure end of 35 sec. Mean duty cycle at six-months increased from 11% to 16%. At 12 months, quality of life and seizure severity scores improved, and responder rate was 50%. Common adverse events were dysphonia (n=7), convulsion (n=6), and oropharyngeal pain (n=3). The authors concluded that the Model 106 performed as intended in the study population, was well tolerated and associated with clinical improvement from baseline. The study design did not allow determination of which factors were responsible for improvements. Study limitations include small sample size (20 patients) and short duration of follow-up (12 months).

Professional Societies

American Academy of Neurology (AAN)

In a practice parameter update on vagus nerve stimulation for epilepsy, the AAN stated that VNS is indicated for adults and adolescents over 12 years of age with medically intractable partial seizures who are not candidates for potentially curative surgical resections, such as lesionectomies or mesial temporal lobectomies. The degree of improvement in seizure control from VNS remains comparable to that of new antiepileptic drugs (AEDs) but is lower than that of mesial temporal lobectomy in suitable surgical resection candidates. Because VNS rarely causes complete seizure remission, and is moderately invasive and expensive, use of VNS is more appropriate in individuals unable to tolerate or benefit from antiepileptic drugs (AEDs), and for whom a partial reduction in seizure frequency will significantly improve their quality of life. Sufficient evidence exists to rank VNS for epilepsy as effective and safe, based on a preponderance of Class I evidence. (Fisher, 1999)

In an evidence based guideline update on vagus nerve stimulation for the treatment of epilepsy (Morris et al., 2013), the AAN makes the following recommendations in addition to those reported in the 1999 assessment:

- VNS may be considered as adjunctive treatment for children with partial or generalized epilepsy (level C). VNS was associated with a greater than 50% reduction in seizure frequency in 55% of 470 children with partial or generalized epilepsy (14 class III studies) but there was significant heterogeneity in the data.
- VNS may be considered in patients with Lennox-Gastaut syndrome (LGS) (level C). VNS was associated with a greater than 50% seizure reduction in 55% of 113 patients with LGS (4 class III studies).
- VNS may be considered progressively effective in patients over multiple years of exposure (level C).
- There should be extra vigilance in monitoring for occurrence of site infection in children. There is evidence of an increase in infection risk at the VNS implantation site in children relative to that in adults.

The AAN defines level C as possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. Level C rating requires at least one Class II study or two consistent Class III studies.

International League Against Epilepsy (ILAE)

A taskforce by the ILAE defines drug resistant epilepsy as a failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. (Kwan et al., 2010; Téllez-Zenteno et al., 2014)

Depression

Kisely et al. (2018) conducted a systematic review and meta-analysis on the effectiveness of deep brain stimulation (DBS) in depression. Ten papers from nine studies met inclusion criteria, all but two of which were double-blinded RCTs. The main outcome was a reduction in depressive symptoms. It was possible to combine data for 190 participants. Patients on active, as opposed to sham, treatment had a significantly higher response and reductions in mean depression score. However, the effect was decreased on some of the subgroup and sensitivity analyses, and there were no differences for most other outcomes. In addition, 84 participants experienced a total of 131 serious adverse effects, although not all could be directly associated with the device or surgery. Finally, publication bias was possible. The authors concluded that DBS may show promise for treatment-resistant depression but remains an experimental treatment until further data are available.

Berry et al. (2013) performed a meta-analysis to compare the response and remission rates in depressed patients with chronic treatment-resistant depression (TRD) treated with vagus nerve stimulation (VNS) plus treatment as usual (VNS+TAU) or TAU. The six clinical studies included in the meta-analysis were two single arm studies of VNS + TAU, a randomized trial of VNS + TAU versus TAU, a single arm study of patients who received TAU, a randomized trial of VNS + TAU comparing different VNS stimulation intensities, and a nonrandomized registry of patients who received either VNS + TAU or TAU. Response was based on the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Clinical Global Impressions scale's Improvement subscale (CGI-I), as these were the two clinician-rated measures common across all or most studies. Outcomes were compared from baseline up to 96 weeks of treatment with VNS +

TAU (n=1035) versus TAU (n=425). MADRS response rate for VNS + TAU at 12, 24, 48, and 96 weeks were 12%, 18%, 28%, and 32% versus 4%, 7%, 12%, and 14% for TAU. The MADRS remission rate for VNS + TAU at 12, 24, 48, and 96 weeks were 3%, 5%, 10%, and 14% versus 1%, 1%, 2%, and 4%, for TAU. Adjunctive VNS Therapy was associated with a greater likelihood of response and remission compared with TAU. For patients who had responded to VNS + TAU at 24 weeks, sustained response was more likely at 48 weeks and at 96 weeks. Similar results were observed for CGI-I response. The authors concluded that for patients with chronic TRD, VNS + TAU has greater response and remission rates that are more likely to persist than TAU. According to the authors, the primary limitation of the meta-analysis involved the individual study designs; namely, that the TAU group data is limited to two trials for the CGI-I scale and one trial for the MADRS scale; in addition, the nonrandomized study and the randomized, sham controlled study represent the only concurrent head-to-head comparisons of VNS + TAU and TAU.

Aaronson et al. (2017) investigated whether adjunctive vagus nerve stimulation (VNS) with treatment as usual in depression has superior long-term outcomes compared with treatment as usual only. This 5-year, prospective, open-label, nonrandomized, observational Treatment-Resistant Depression Registry study was conducted at 61 U.S. sites and included 795 patients who were experiencing a major depressive episode (unipolar or bipolar depression) of at least 2 years' duration or had three or more depressive episodes (including the current episode), and who had failed four or more depression treatments (including ECT). Patients with a history of psychosis or rapid-cycling bipolar disorder were excluded. The primary efficacy measure was response rate, defined as a decrease of ≥50% in baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score at any post-baseline visit during the 5-year study. Secondary efficacy measures included remission. Patients had chronic moderate to severe depression at baseline. The registry results indicate that the adjunctive VNS group had better clinical outcomes than the treatment-as-usual group, including a significantly higher 5-year cumulative response rate (67.6% compared with 40.9%) and a significantly higher remission rate (cumulative first-time remitters, 43.3% compared with 25.7%). A subanalysis demonstrated that among patients with a history of response to ECT, those in the adjunctive VNS group had a significantly higher 5-year cumulative response rate than those in the treatment-as-usual group (71.3% compared with 56.9%). A similar significant response differential was observed among ECT nonresponders (59.6% compared with 34.1%). According to the authors, this registry represents the longest and largest naturalistic study of efficacy outcomes in treatment-resistant depression, and it provides additional evidence that adjunctive VNS has enhanced antidepressant effects compared with treatment as usual in this severely ill patient population. The authors indicted there were several important limitations to this registry design. Given ethical concerns about following such a severely ill patient population over a 5-year period, the registry had a naturalistic, observational design and did not randomly assign patients to the treatment groups. Similarly, the treatment assignment in the registry was not blinded, in part because it would have been unethical to implant a sham device for a long duration in severely ill patients.

A Comparative Effectiveness Review was prepared for the Agency for Healthcare Research and Quality (AHRQ) on Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. The report identified only one study (Rush et al., 2005) comparing VNS to sham, conducted in a Tier 1 major depressive disorder (MDD)/bipolar mix population. According to the AHRQ report, the majority of measures used by this study found no difference between VNS and sham on changes in depressive severity or rates of response and remission. Since only a single study was identified for this comparison, further assessment by key variables was not possible. (Gaynes et al., 2011)

In a 2009 guidance document, the National Institute for Health and Care Excellence (NICE) stated that the current evidence on the safety and efficacy of vagus nerve stimulation (VNS) for treatment resistant depression is inadequate in quantity and quality. Therefore this procedure should be used only with special arrangements for clinical governance, consent and audit or research. It should be used only in patients with treatment-resistant depression. (NICE, 2009)

Professional Societies

American Psychiatric Association (APA)

In a clinical practice guideline for the treatment of patients with major depressive disorder, the APA states that electroconvulsive therapy remains the treatment of best established efficacy against which other stimulation treatments (e.g., VNS, deep brain stimulation, transcranial magnetic stimulation, other electromagnetic stimulation therapies) should be compared. The APA states that vagus nerve stimulation (VNS) may be an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT [III]. For patients whose depressive episodes have not previously responded to acute or continuation treatment with medications or a depression focused psychotherapy but who have shown a response to ECT, maintenance ECT may be considered [III]. Maintenance treatment with VNS is also appropriate for individuals whose symptoms have responded to this treatment modality [III]. According to the APA, relative to other antidepressive treatments, the role of VNS remains a subject of debate. However, it could be considered as an option for patients with substantial symptoms that have not responded to repeated trials of antidepressant treatment. The three APA rating categories represent varying levels of clinical confidence:

- I: Recommended with substantial clinical confidence
- II: Recommended with moderate clinical confidence

- III: May be recommended on the basis of individual circumstances

(Gelenberg et al., 2010; Reaffirmed October 31, 2015)

Canadian Network for Mood and Anxiety Treatments (CANMAT)

In 2016, the Canadian Network for Mood and Anxiety Treatments (CANMAT) revised the 2009 evidence-based clinical guidelines for the treatment of depressive disorders guidelines by updating the evidence and recommendations. The scope of the 2016 guidelines remains the management of major depressive disorder (MDD) in adults, with a target audience of psychiatrists and other mental health professionals. Using the question-answer format, the authors conducted a systematic literature search focusing on systematic reviews and meta-analyses. Evidence was graded using CANMAT-defined criteria for level of evidence. Recommendations for lines of treatment were based on the quality of evidence and clinical expert consensus. "Neurostimulation Treatments" is the fourth of six sections of the 2016 guidelines. Evidence-informed responses were developed for 31 questions for 6 neurostimulation modalities: 1) transcranial direct current stimulation (tDCS), 2) repetitive transcranial magnetic stimulation (rTMS), 3) electroconvulsive therapy (ECT), 4) magnetic seizure therapy (MST), 5) vagus nerve stimulation (VNS), and 6) deep brain stimulation (DBS). Most of the neurostimulation treatments have been investigated in patients with varying degrees of treatment resistance. The authors concluded that there is increasing evidence for efficacy, tolerability, and safety of neurostimulation treatments. rTMS is now a first-line recommendation for patients with MDD who have failed at least 1 antidepressant. ECT remains a second-line treatment for patients with treatment-resistant depression, although in some situations, it may be considered first line. Third-line recommendations include tDCS and VNS. MST and DBS are still considered investigational treatments. (Milev et al., 2016)

Other Conditions

The use of vagus nerve stimulation has been investigated for other conditions including Alzheimer’s disease (Merrill et al., 2006), anxiety (George et al., 2008), autism spectrum disorder (Levy et al., 2010), obsessive-compulsive disorder (George et al., 2008), pain (Napadow et al., 2012), headaches (Pintea et al., 2017; Cecchini et al., 2009), sleep disorders (Jain et al., 2014), heart disease/congestive heart failure (De Ferrari et al., 2017; Gold et al., 2016: Zannad et al., 2015; Premchand et al., 2016), asthma (Steyn et al., 2013; Miner et al., 2012), fibromyalgia (Lange et al., 2011), and other psychiatric disorders. (Cimpianu et al.,2017) However, because of limited studies, small sample sizes and weak study designs, there is insufficient data to conclude that vagus nerve stimulation is safe and/or effective for treating these indications. Further clinical trials demonstrating the clinical usefulness of vagus nerve stimulation are necessary before it can be considered proven for these conditions.

<u>Transcutaneous (Nonimplantable) Vagus Nerve Stimulation</u>

Cluster Headache

Goadsby et al. (2018) compared non-invasive vagus nerve stimulation (nVNS) with a sham device for acute treatment in patients with episodic or chronic cluster headache (CH) (eCH, cCH). After completing a 1-week run-in period, subjects were randomly assigned (1:1) to receive nVNS or sham therapy during a 2-week double-blind period. The primary efficacy endpoint was the proportion of all treated attacks that achieved pain-free status within 15 minutes after treatment initiation, without rescue treatment. The Full Analysis Set comprised 48 nVNS-treated (14 eCH, 34 cCH) and 44 sham-treated (13 eCH, 31 cCH) subjects. For the primary endpoint, nVNS (14%) and sham (12%) treatments were not significantly different for the total cohort. In the eCH subgroup, nVNS (48%) was superior to sham (6%). No significant differences between nVNS (5%) and sham (13%) were seen in the cCH subgroup. Combining both eCH and cCH patients, nVNS was no different to sham. The authors concluded that for the treatment of CH attacks, nVNS was superior to sham therapy in eCH but not in cCH. According to the authors, this study had limitations, including its short duration, which did not allow for evaluation of continued/change in response with long-term nVNS therapy. Another study limitation was the imbalance between CH subtypes, with the eCH subgroup comprising <30% of subjects. During the open-label period, subjects could alter their CH treatment regimens by adding prophylactic therapies, or changing doses of existing treatments, or both. According to the authors, this stipulation confounded the results, making it impossible to discern whether changes in efficacy outcomes were attributable to nVNS therapy or to other changes in treatment during this period.

Gaul et al. (2017) evaluated additional patient-centric outcomes, including the time to and level of therapeutic response, in a post hoc analysis of the PREVA study (Gaul et al., 2016). After a 2-week baseline phase, 97 patients with chronic cluster headache entered a 4-week randomized phase to receive non-invasive vagus nerve stimulation plus standard of care (nVNS + SoC) (n = 48) or SoC alone (n = 49). All 92 patients who continued into a 4-week extension phase received nVNS + SoC. Compared with SoC alone, nVNS + SoC led to a significantly lower mean weekly attack frequency by week 2 of the randomized phase; the attack frequency remained significantly lower in the nVNS + SoC group through week 3 of the extension phase. Attack frequencies in the nVNS + SoC group were significantly lower at all study time points than they were at baseline. Response rates were significantly greater with nVNS + SoC than with SoC alone when response was defined as attack frequency reductions of ≥25%, ≥50%, and ≥75% from baseline. The authors concluded that prophylactic nVNS led to rapid, significant, and sustained reductions in chronic cluster headache attack frequency within 2 weeks after its addition to SoC and was associated with significantly higher ≥25%, ≥50%, and ≥75% response rates than SoC alone. The rapid decrease in weekly attack frequency justifies a 4-week trial period to identify responders to nVNS, with a high degree of confidence, among patients with chronic cluster headache. Of note, the 100% response rate was 8% with nVNS + SoC and 0% with SoC alone. This study examined the prophylactic use of non-invasive vagus nerve stimulation but did not control for placebo effect and lacked data beyond four weeks.

Gaul et al. (2016) evaluated non-invasive vagus nerve stimulation (nVNS) as an adjunctive prophylactic treatment of chronic cluster headache (CH) in a prospective, open-label, randomized study (PREVA Trial) that compared adjunctive prophylactic nVNS (n = 48) with standard of care (SoC) alone (control (n = 49)). A two-week baseline phase was followed by a four-week randomized phase (SoC plus nVNS vs control) and a four-week extension phase (SoC plus nVNS). The primary end point was the reduction in the mean number of CH attacks per week. Response rate, abortive medication use and safety/tolerability were also assessed. During the randomized phase, individuals in the intent-to-treat population treated with SoC plus nVNS (n = 45) had a significantly greater reduction in the number of attacks per week vs controls (n=48) for a mean therapeutic gain of 3.9 fewer attacks per week. Higher ≥50% response rates were also observed with SoC plus nVNS vs controls. No serious treatment-related adverse events occurred. The authors concluded that adjunctive prophylactic nVNS is a well-tolerated novel treatment for chronic CH, offering clinical benefits beyond those with standard of care. Study limitations include the lack of a placebo or sham device, an open-label study design, the short treatment duration, and the use of patient-reported outcomes.

Silberstein et al. (2016a) evaluated non-invasive vagus nerve stimulation (nVNS) as an acute cluster headache (CH) treatment. One hundred fifty subjects were enrolled and randomized (1:1) to receive nVNS or sham treatment for ≤1 month during a double-blind phase; completers could enter a 3-month nVNS open-label phase. The primary end point was response rate, defined as the proportion of subjects who achieved pain relief (pain intensity of 0 or 1) at 15 minutes after treatment initiation for the first CH attack without rescue medication use through 60 minutes. Secondary end points included the sustained response rate (15-60 minutes). Subanalyses of episodic cluster headache (eCH) and chronic cluster headache (cCH) cohorts were prespecified. The intent-to-treat population comprised 133 subjects: 60 nVNS-treated (eCH, n=38; cCH, n=22) and 73 sham-treated (eCH, n=47; cCH, n=26). A response was achieved in 26.7% of nVNS-treated subjects and 15.1% of sham-treated subjects. Response rates were significantly higher with nVNS than with sham for the eCH cohort (nVNS, 34.2%; sham, 10.6%) but not the cCH cohort (nVNS, 13.6%; sham, 23.1%). Sustained response rates were significantly higher with nVNS for the eCH cohort and total population. Adverse device effects (ADEs) were reported by 35/150 (nVNS, 11; sham, 24) subjects in the double-blind phase and 18/128 subjects in the open-label phase. No serious ADEs occurred. The authors indicated that non-invasive vagus nerve stimulation is a safe and well-tolerated treatment that represents a novel and promising option for eCH. According to the authors, study limitations include the analysis of the cCH cohort as part of the primary end point, the need for careful interpretation of subanalyses results, challenges with blinding inherent in medical device studies, and the time to first measurement of response used to define the primary efficacy end point.

Migraine Headache

Tassorelli et al. (2018) evaluated the efficacy, safety, and tolerability of noninvasive vagus nerve stimulation (nVNS; gammaCore; electroCore, LLC,) for the acute treatment of migraine in a multicenter, double-blind, randomized, sham-controlled trial. A total of 248 participants with episodic migraine with/without aura were randomized to receive nVNS or sham within 20 minutes from pain onset. Participants were to repeat treatment if pain had not improved in 15 minutes. nVNS (n = 120) was superior to sham (n = 123) for pain freedom at 30 minutes (12.7% vs 4.2%) and 60 minutes (21.0% vs 10.0%) but not at 120 minutes (30.4% vs 19.7%) after the first treated attack. A post hoc repeated-measures test provided further insight into the therapeutic benefit of nVNS through 30, 60, and 120 minutes. nVNS demonstrated benefits across other endpoints including pain relief at 120 minutes and was safe and well-tolerated. The authors concluded that this randomized sham-controlled trial supports the abortive efficacy of nVNS as early as 30 minutes and up to 60 minutes after an attack. Findings also suggest effective pain relief, tolerability, and practicality of nVNS for the acute treatment of episodic migraine. According to the authors, the role of nVNS in migraine therapy is being further explored in ongoing large-scale, randomized, sham-controlled trials with long-term follow-up.

Silberstein et al. (2016b) evaluated the feasibility, safety, and tolerability of noninvasive vagus nerve stimulation (nVNS) for the prevention of chronic migraine (CM) attacks. In this prospective, multicenter, double-blind, sham-controlled pilot study of nVNS in CM prophylaxis, adults with CM (≥15 headache d/mo) entered the baseline phase (1 month) and were subsequently randomized to nVNS or sham treatment (2 months) before receiving open-label nVNS treatment (6 months). The primary endpoints were safety and tolerability. Efficacy endpoints in the intent-to-treat population included change in the number of headache days per 28 days and acute medication use. Fifty-nine participants (mean age, 39.2 years; mean headache frequency, 21.5 d/mo) were enrolled. During the randomized phase, tolerability was similar for nVNS (n = 30) and sham treatment (n = 29). Most adverse events were mild/moderate and transient. Mean changes in the number of headache days were -1.4 (nVNS) and -0.2 (sham). Twenty-seven participants completed the open-label phase. For the 15 completers initially assigned to nVNS, the mean change from baseline in headache days after 8 months of treatment was -7.9. The authors concluded that therapy with nVNS was well-tolerated with no safety issues. Study limitations included the small sample size, blinding challenges, and high discontinuation rate. According to the authors, larger sham-controlled studies are needed.

In a monocentric, randomized, controlled, double-blind study, Straube et al. (2015) assessed the efficacy and safety of transcutaneous stimulation of the auricular branch of the vagal nerve (t-VNS) in the treatment of chronic migraine. After one month of baseline, chronic migraine patients were randomized to receive 25 Hz or 1 Hz stimulation of the sensory vagal area at the left ear by a handhold battery driven stimulator for 4 h/day during 3 months. Headache days per 28 days were compared between baseline and the last month of treatment and the number of days with acute medication was recorded The Headache Impact Test (HIT-6) and the Migraine Disability Assessment (MIDAS) questionnaires were used to assess headache-related disability. Of 46 randomized patients, 40 finished the study (per protocol). In the per protocol analysis, patients in the 1 Hz group had a significantly larger reduction in headache days per 28 days than patients in the 25 Hz group. 29.4 % of the patients in the 1 Hz group had a ≥50 % reduction in headache days vs. 13.3 % in the 25 Hz group. HIT-6 and MIDAS scores were significantly improved in both groups, without group differences. There were no serious treatment-related adverse events. The authors concluded that treatment of chronic migraine by t-VNS at 1 Hz was safe and effective. This study was limited by a small sample size.

The National Institute for Health and Care Excellence (NICE) has published a guideline addressing transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine. The guideline states that current evidence on the safety of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine raises no major concerns. The evidence on efficacy is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. (NICE, 2016)

Professional Societies

American Headache Society (AHS)

The AHS guideline on the treatment of cluster headache does not include specific recommendations for noninvasive vagus nerve stimulation. The guideline notes that future sham-controlled blinded trials are warranted to elucidate the efficacy and safety of nVNS for the treatment of cluster headache. (Robbins et al., 2016)

Other Conditions

Transcutaneous vagus nerve stimulation has been investigated for other conditions including atrial fibrillation (Stavrakis et al., 2015), epilepsy (Barbella et al., 2018; Bauer et al., 2016), depression (Liu et al., 2016; Fang et al., 2016; Hein, et al., 2013; Rong, et al., 2016), impaired glucose tolerance (Huang et al., 2014), schizophrenia (Osoegawa et al., 2018), tinnitus. (Ylikoski et al., 2017; Kreuzer et al., 2014) Due to limited studies, small sample sizes and weak study designs, there is insufficient data to conclude that transcutaneous vagus nerve stimulation is safe and/or effective for treating these indications. Further clinical trials demonstrating the clinical usefulness of these devices are necessary before it can be considered proven for these conditions.

Additional Search Terms

Neuromodulation, pneumogastric nerve, non-implantable vagus nerve stimulation devices.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Implantable Vagus Nerve Stimulators

The FDA approved the NeuroCybernetic Prosthesis (NCP)® System (Cyberonics, Inc.) in July 1997 (P970003) for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with medically refractory, partial-onset seizures. In 2017, this approval was extended for use in patients 4 years of age and older. See the following websites for more information:

- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P970003S207.
- http://www.accessdata.fda.gov/cdrh_docs/pdf/p970003.pdf.

(Accessed July 2, 2018)

In July 2005, the VNS Therapy™ System (Cyberonics, Inc.) was approved for marketing by the FDA for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments. (PMA Supplement 50) Available at:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P970003S050. (Accessed July 2, 2018)

The VNS Therapy System (Cyberonics now known as LivaNova) received initial FDA Premarket Approval (PMA 970003) on July 16, 1997. The original FDA PMA was granted for VNS Therapy system as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years old. Many supplemental approvals have been issued for this system since the original approval. On June 23, 2017, LivaNova received FDA approval (P970003/S207) of its

VNS Therapy system for use as an adjunctive therapy in reducing the frequency of seizures in persons four years of age and older with partial onset seizures that are refractory to antiepileptic medications. See the following websites for more information:

- https://www.accessdata.fda.gov/cdrh_docs/pdf/p970003.pdf.
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P970003.

(Accessed June 21, 2018)

The AspireSR Model 106 generator received FDA premarket approval in May 2015 (PMA P970003). The AspireSR is part of Cyberonics's (now known as LivaNova) VNS Therapy System. The AspireSR Model 106 has an additional, optional mode called AutoStim Mode or Automatic Stimulation. This mode monitors and detects tachycardia heart rates, which may be associated with an impending seizure, and automatically delivers stimulation to the vagus nerve. See the following websites for more information:

- http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P970003S173.
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=353134.

(Accessed July 2, 2018)

Transcutaneous (Nonimplantable) Vagus Nerve Stimulation Devices

On April 14, 2017, the FDA granted a de novo request that allows the gammaCore® device to be marketed in the U.S. for the treatment of acute pain associated with episodic cluster headache in adults. According to the FDA, the gammaCore Non-invasive Vagus Nerve Stimulator is intended to provide noninvasive vagus nerve stimulation (nVNS) on the side of the neck. The FDA determined that this device should be classified into class II. See the following website for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf15/den150048.pdf.
(Accessed July 2, 2018)

On January 23, 2018, the FDA expanded indications for the gammaCore (electroCore LLC) noninvasive vagus nerve stimulator to include the acute treatment of pain associated with migraine headaches in adults. See the following website for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K173442.pdf. (Accessed June 21, 2018)

To locate marketing clearance information for a specific device or manufacturer, search the Center for Devices and Radiological Health (CDRH) 510(k) database or the Premarket Approval (PMA) database by product and/or manufacturer name.

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The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [*2019T0101X*]

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
01/01/2019	• Reorganized policy template: ○ Simplified and relocated *Instructions for Use* ○ Removed *Benefit Considerations* section • Simplified coverage rationale (no change to guidelines) • Archived previous policy version SURGERY 073.15 T2

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

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